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# EFFECTS OF CHOLINERGIC DRUGS ON EXERCISE FERFORMANCE AND SIMPLE REACTION TIME OF RHESUS MONKEYS

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Four juvenile rhesus monkeys were trained to perform an exercise response and respond aperiodically to a visual signal. The exercise response simulated a rowing motion and typically resulted in heart rates in excess of 200 beats per minute. A red signal light was usually displayed during the exercise period. Using a partial reinforcement schedule, the red light was replaced aperiodically with a green signal light that indicated a reaction-time condition. Responses on a lever within 1 s of the green light onset resulted in a food pellet. The drugs atropine sulfate, pralidoxime chloride, pyridostigmine bromide, scopolamine hydrobromide, and meclizine hydrochloride were administered concurrently or individually before the exercise session. Atropine sulfate and pralidoxime hydrochloride were administered in three dose levels. The concurrent drug administration produced significant dose-related decrements in exercise responses and increases in postreinforcement pause times. Tail temperatures during drug testing generally were below baseline temperatures. Only atropine sulfate, when tested

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individually, produced behavioral effects. Neither concurrent nor individual administration of the drugs produced any reaction-time change. The availability of tapwater during training and drug testing sessions did not alter atropine sulfate effects on performance. (SDW)

## SUMMARY PAGE

### THE PROBLEM

Naval personnel, trained to face nerve-agent threats, may prematurely administer pretreatment and/or antidote drugs. The side effects of hasty pretreatment and antidote drug use may reduce overall performance. Both physical and cognitive ability may be affected and thereby reduce mission capability. Also, the interaction of antidote drugs with those prescribed for other reasons, such as motion-sickness treatment, may produce additional performance degradation.

To determine the effects of antidotes and other compounds, four male rhesus monkeys were trained to perform a strenuous physical exercise task and respond to aperiodic visual stimuli. A pretreatment drug, pyridostigmine bromide, and three dose levels of nerve-agent antidotes, atropine sulfate and pralidoxime chloride, were tested for effects on monkey performance. In addition, the antimotion sickness compounds, scopolamine hydrobromide and meclizine hydrochloride, were tested.

### FINDINGS

Significant dose-related decrements in exercise responses and increases in postreinforcement pause times were observed when the drugs were administered concurrently. Only atropine sulfate, when tested individually, produced behavioral effects. Neither concurrent nor individual administration of the drugs produced any change in reaction time to visual stimuli.

### RECOMMENDATIONS

Premature use of atropine sulfate as a nerve-agent antidote may prove detrimental to physical performance of naval personnel. Although this drug did not alter reaction times of monkeys to simple visual stimuli, its effects on overall cognitive capability warrant further study.


### Acknowledgments

We thank Pfizer, Inc., Brooklyn, New York, for donating the meclizine HCL used in this study. A special thanks is given to Robert Upchurch for the dedicated care and training given the animals used in this study. We also thank Robert Barrett, Chuck Mogensen, and Anna Johnson for their assistance in the preparation of the manuscript.

## INTRODUCTION

Organophosphates are present in many insecticides, as well as the nerve agents tabun, sarin, soman, and VX, and strongly inhibit acetylcholinesterase (AChE). This enzyme (AChE) is necessary to break down acetylcholine (ACh), which is released at many autonomic and central nervous system nerve endings. When AChE is inhibited, excess ACh accumulates at nerve endings, thereby producing continued discharges at neuromuscular junctions or neural synapses. In severe cases, AChE inhibition results in respiratory distress, gastrointestinal disorders, convulsions, and death. Conventional treatment of organophosphate poisoning relies on anticholinergic antidotes such as atropine sulfate and oximes such as pralidoxime chloride (2-PAM) to reactivate AChE (1).

Pretreatment to protect AChE before organophosphate exposure is preferable. The carbamate pyridostigmine bromide, which is also an AChE inhibitor, has been used to temporarily bind AChE and protect it from organophosphates (2). Reversal of the carbamate-AChE bond allows free enzyme to reduce ACh buildup at nerve endings and reduce the effects of organophosphate intoxication. Effective carbamate prophylaxis, however, requires postexposure treatment with atropine and an oxime.

Pretreatment and antidote drugs can have detrimental effects on human performance (3,4), particularly when they are used in the absence of organophosphate challenge. Following a literature review of the performance decrements produced by these drugs, Headly (4) concluded that inadvertent use can be debilitating, depending on dosage and task specificity. For example, low doses of atropine may produce poor cognitive-task performance while higher doses may also disrupt the capacity for strenuous physical exercise. Comparatively, the side effects of 2-PAM are mild and have little effect on task performance.

While the literature is extensive on the effects of pretreatment and antidote drugs on performance, relatively little is known regarding the effects of these compounds administered concurrently. Furthermore, the effect of such compounds administered concurrently to exercising subjects is unknown. Also, pretreatment and antidotal compounds may interact with drugs previously taken for other therapeutic purposes. To determine the nteractive effects of drug combinations on the cognitive performance of exercising monkeys, atropine and 2-PAM were administered at several dosages simultaneously (experiment I) and individually (experiment II) along with pyridostigmine. In each experiment, the antimotion sickness therapeutic drugs meclizine hydrochloride and scopolamine hydrobromide were also tested with the pretreatment and antidote drugs. An additional experiment (experiment III) was conducted to determine if tap water would alleviate symptoms, such as "dry mouth," produced by the anticholinergic drugs and improve exercise performance of the monkeys.

## METHODS AND MATERIALS

### SUBJECTS

Four male juvenile rhesus monkeys (*Macaca mulatta*) with a mean weight of 3.04 kg (range 2.88-3.23 kg) at the beginning of the drug sessions were used in experiments I and II. Four additional cohorts with a mean weight of 3.42 kg (range 2.96-3.75 kg) were used as subjects for experiment III. All monkeys were obtained from the Naval Aerospace

Medical Research Laboratory breeding colony located in Pensacola, Florida. The subjects were fed a standard primate diet (Wayne Co., 24% protein) daily in sufficient quantities (freely available in their cages) to promote normal growth for a monkey of that age and housing condition. Prior to training, the animals were fed a reduced amount of the same diet daily until their body mass was reduced by 10% of the previously determined ad libitum weight. During the course of the experiments, the monkeys were maintained at this weight except for periods where they were again free-fed for several days (5-7) to establish a new ad libitum weight. This procedure resulted in healthy, well-conditioned animals that worked adequately on food-reinforced tasks. The animals obtained their daily food ration (Noyes Co., 750 mg monkey formula L pellets) while performing the experiment. Their diet during the experiments was supplemented only with fresh fruit. Water was continuously available in the home cage. Monkeys in the home cages were kept in the vivarium under a 12/12-h light-dark cycle (0700 h on, 1900 h off) at 22.6 °C (± 0.78 *SEM*).

## APPARATUS

An exercise chair, designed basically as described by Knepton et al. (5) (Fig. 1), was constructed of Plexiglas and aluminum. It held the monkey in an upright seated position by a plastic neck restraint and a Velcro waistband. The monkeys were placed in the chair for not more than 75 min per day. Limb movements by the monkey, which simulated a rowing motion, were required to move hand and foot pedals against a 1-kg spring load. Microswitches mounted on the chair detected forward and reverse movements of the hand and foot pedals. Signal lamps (GE-757) were mounted in a plastic enclosure behind 4.5-cm squares of green and red translucent Plexiglas and placed 20 cm in front of the monkey at eye level. When illuminated, these served as discriminative stimuli for exercise or reaction-time conditions. A response lever was mounted on the chair directly in front of the monkey and was used to determine reaction time.

The exercise chair was placed inside a metal sound-attenuating chamber (1.26 m high x 0.61 m wide x 1.22 m deep interior dimensions), which was ventilated by an electric fan at 20 cubic meters per minute. An overhead fluorescent lamp (27 W Vita-Lite) was used to illuminate the interior of the chamber, and a speaker (30-cm diameter) was used to provide a white masking noise (73 dBA). A pellet feeder was mounted on top of the chamber and delivered food pellets via Tygon tubing to a plastic cup at mouth level in front of the monkey.

A PDP-8A minicomputer was used to determine schedule contingencies, control discriminative stimuli, deliver food pellets, and record behavioral and heart-rate data. During some training sessions, heart rate was monitored using two silver/silver chloride electrodes (Del Mar Avionics No. 18366) fastened to the monkey's back with adhesive circles (lumbar region, 0.8 cm lateral to the vertebral column) and an electrocardiogram monitor (Hewlett Packard No. 78203C). Typically, heart rate increased from resting values of 100-140 to 200-240 beats per minute during exercise. Temperature at the dorsal skin surface midway down the monkey's tail (Yellow Springs Probe 409B) and ceiling air temperature of the chamber (Yellow Springs Probe 405) were recorded at the beginning and end of each session component using analog temperature monitors (Yellow Springs No. 43T-J).

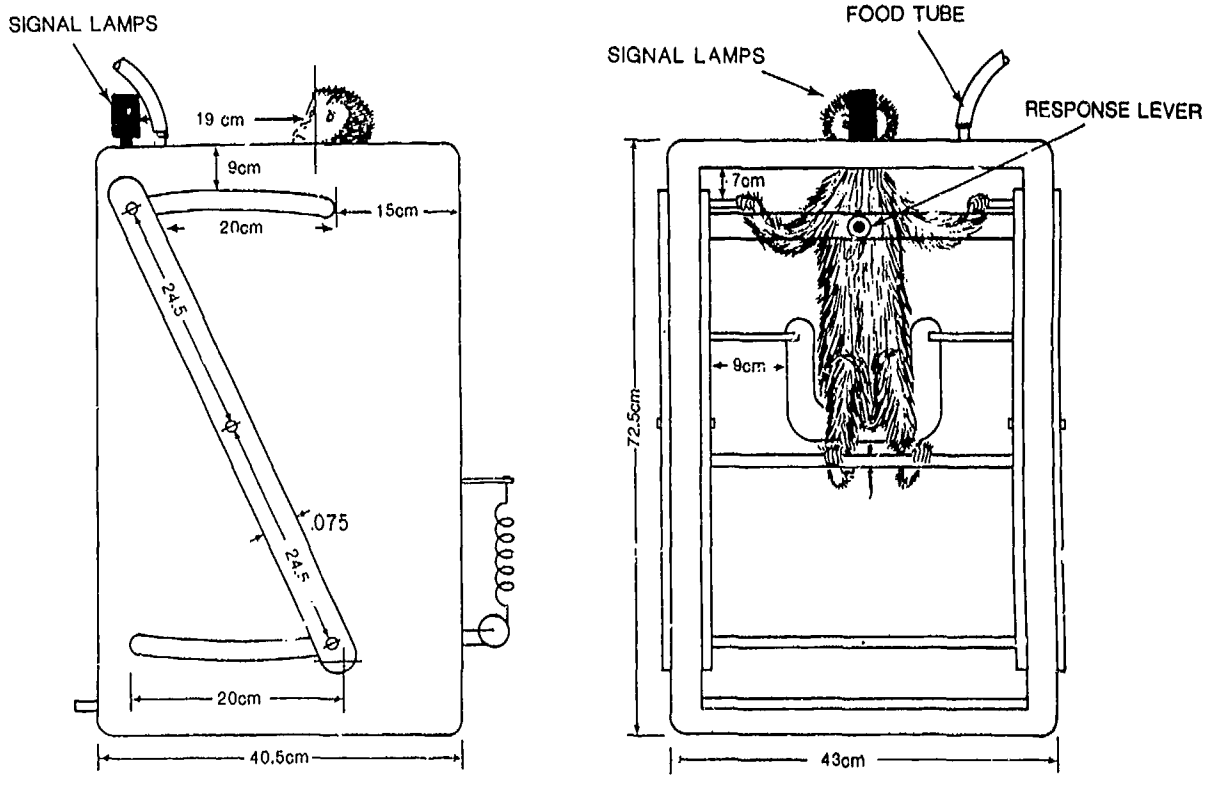


**Figure 1.** *Representation of a rhesus monkey in the exercise chair showing exercise handles on the side, light panel on top of the chair to present visual stimuli, and a reaction time lever mounted directly in front of the animal.*

## OPERANT TRAINING

The monkeys were trained to perform the exercise motion in the presence of a red signal lamp. The red signal was extinguished aperiodically using a random ratio schedule (RR-12; a probability of 0.085 for every exercise response), and a green signal lamp was turned on. If the green light was followed by a response on the center lever within 1 s, a food pellet was delivered. Reaction time was measured from onset of the green signal to closure of a microswitch by a lever response. A reaction time longer than 1 s did not result in food pellet delivery. The operant test session was 75 min long and was composed of seven components: an initial 15-min adaptation component followed by three 15-min exercise components each of which was followed by a 5-min rest component. During the adaptation and rest components of the schedule, the overhead light and discriminative stimuli were turned off. Total exercise responses, mean reaction time, and mean postreinforcement pause time were recorded for baseline and drug test sessions.

## DRUGS

The drugs given in each experiment are summarized in Fig. 2 and briefly described below. In each experiment, three dosages of atropine sulfate (0.03, 0.05, and 0.09 mg/kg) and pralidoxime chloride (2-PAM) (8.6, 15.3, and 27.2 mg/kg) were used as antidotes. Pyridostigmine bromide at a dosage of 0.43 mg/kg was used as the pretreatment drug. Meclizine hydrochloride at a dosage of 0.71 mg/kg and scopolamine hydrobromide at a dosage of 0.008 mg/kg were used as therapeutic drugs. Three drug combinations were tested in this study: (1) pyridostigmine, atropine, and 2-PAM; (2) pyridostigmine, atropine, 2-PAM, and scopolamine; and (3) pyridostigmine, atropine, 2-PAM, and meclizine. In each combination, only one dosage of the antidotes (1, 2, or 3) was given per session (i.e., atropine/0.03 mg/kg and 2-PAM/8.6 mg/kg).

A double-blind procedure was used to administer all drugs to the monkeys. The pretreatment (pyridostigmine) and therapeutic drugs (scopolamine and meclizine) were administered 30 min before the administration of antidotes. The antidotes (atropine and 2-PAM) were administered 30 min prior to onset of the operant session. All drugs, except meclizine, were administered intramuscularly in the lateral thigh with physiological saline as the vehicle. Solutions were prepared as injection volumes of 0.3 ml/kg except for the highest dose of pralidoxime chloride, which had an injection volume of 0.5 ml/kg. Meclizine was administered orally by mixing the prescribed dose of the drug with 1 g of peanut butter smeared on 1/2 of a monkey biscuit. Sham drug treatments consisted of either saline injections or peanut butter on a biscuit given orally.

Only one drug or drug combination was given per week. At the completion of experiment II, blood samples were collected from the femoral vein of four monkeys before the administration of pyridostigmine and again after the completion of the operant session. Blood samples were then analyzed for red blood cell and plasma cholinesterase by an automated chemistry system (Baker Centrichem 600) following the method of Ellman et al. (6).

DRUG SUMMARY CHART

| Pretreatment | Antidotes | Therapeutic |
|---|---|---|
| PY - Pyridostigmine bromide (0.4 mg/kg) | AT - Atropine sulfate (0.03, 0.05, 0.09, mg/kg) | ME - Meclizine hydrochloride (0.7 mg/kg) |
| | PR - Pralidoxime chloride (2-PAM) (8.6, 15.3, 27.2 mg/kg) | SC - Scopolamine hydrobromide (0.008 mg/kg) |

DRUG COMBINATION AND DELIVERY CHART

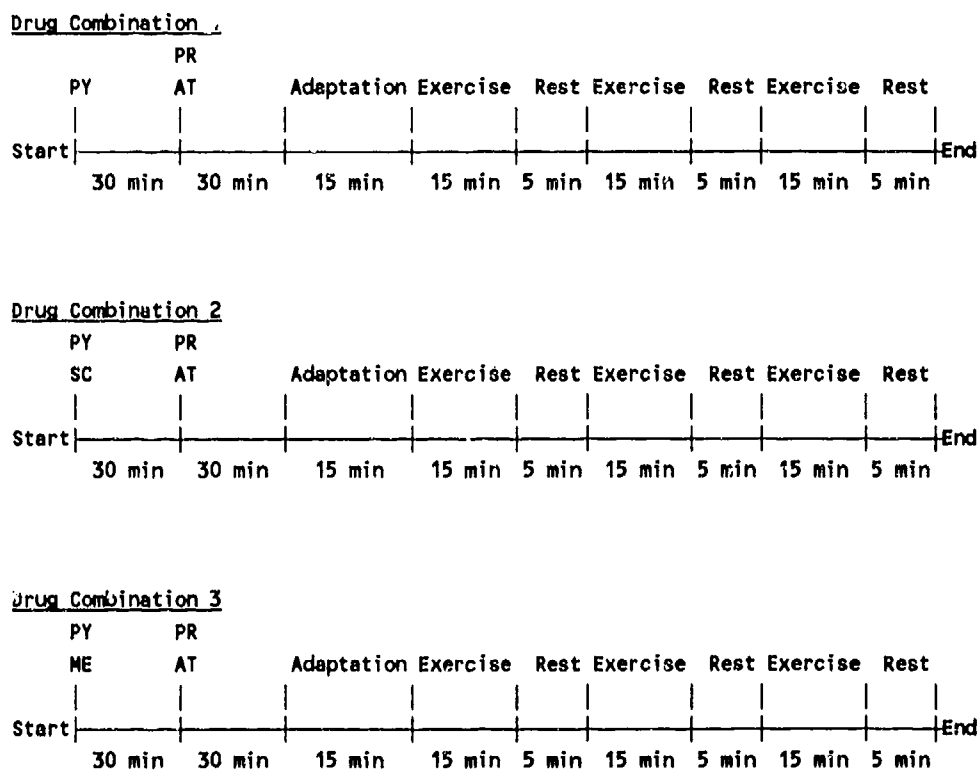


**Figure 2.** *Summary of the drug combinations and time of delivery prior to drug test sessions. Dosages are given in parentheses.*

## PROCEDURE

Once exercise stabilized (less than 10% intersession variability), drug testing was initiated. All tests were given using a repeated-measures experimental design with the order of drugs and dosages randomized. In experiment I, different combinations of the pretreatment and therapeutic drugs and one dosage of the antidote drugs were administered prior to an operant session as described above. In a random order, each monkey was tested at each of the antidote dosages (atropine and 2-PAM). In experiment II, only a single drug was administered prior to each operant session at the same dosages and time intervals for drug delivery as used in experiment I. Experiment III was a replication of experiment I (drug combination 1), except that a 1-liter glass bottle filled with tap water and fitted with a primate stainless steel lick tube was mounted to the exercise chair and was available to the monkey during training and drug sessions.

## RESULTS

The data for each drug session were transformed to percentage of baseline scores using data from the session the day prior to drug exposure as baseline. The scores (percentage of baseline) for each dependent variable were then analyzed using either a one- or two-factor repeated measures analysis of variance. Reliable effects were evaluated further with Duncan's Range test (7). All tests for significance were evaluated at $p < 0.05$ or less.

### CHOLINESTERASE ACTIVITY

Blood samples collected before and after an operant session showed a decrease in cholinesterase. The dose of pyridostigmine (0.43 mg/kg) produced a decrease of both red blood cell cholinesterase (59.9% ± 4.7 *SEM*) and plasma cholinesterase (74.3% ± 1.6 *SEM*).

### BEHAVIORAL EFFECTS

Experiment I. Cumulative records of the exercise responses for a baseline and three drug sessions from monkey 2N7 are shown in Fig. 3. The exercise rate for each exercise component of the baseline session was steady with relatively few pauses. The drug combination pyridostigmine, atropine, and 2-PAM, however, led to reduced exercise responses and very long pause times as the dosage of the drugs (atropine and 2-PAM) was increased, as indicated by drug doses 1, 2, and 3. The largest dose given to monkey 2N7 resulted in a complete cessation of exercise responses during the third exercise component (Fig. 3, session 89).

Mean exercise responses as a percentage of baseline responses for the drug and sham sessions are shown in Fig. 4. The sham treatments did not significantly affect exercise, which remained virtually the same as baseline performance (100%). The drug combinations, however, showed highly reliable effects for dosage, $F(3, 9) = 49.67, p < 0.001$, and drug combination, $F(2, 6) = 12.88, p < 0.01$. The drugs caused a nearly linear decrease in exercise responses with increasing dosage as confirmed by a product moment correlation coefficient ($r = -.87, p < 0.01$). The addition of scopolamine to the drug combination caused an additional decrease in exercise responses, which was statistically significant only for dosage 2 ($p < 0.05$) while meclizine had no additional effect.

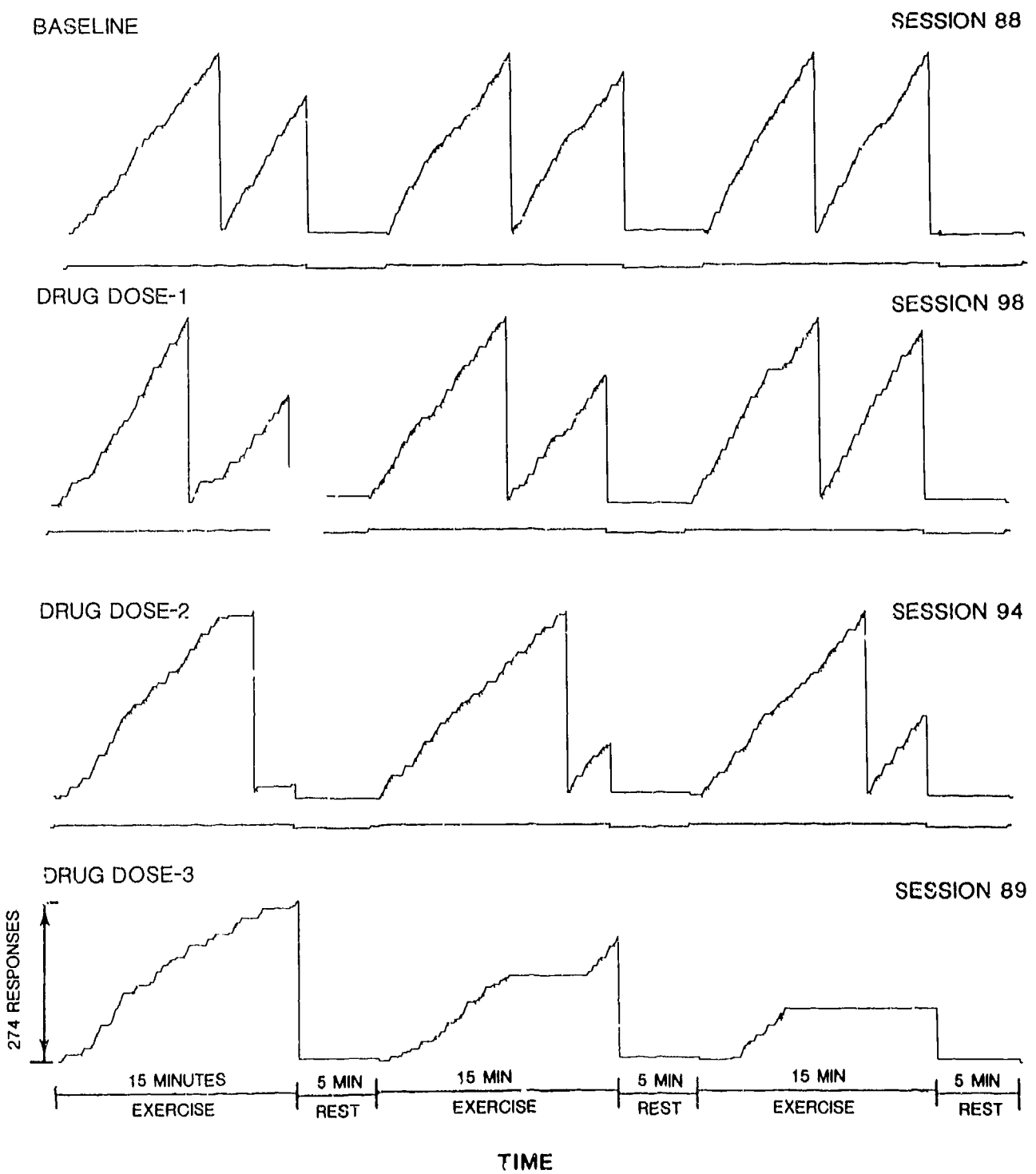


**Figure 3.** *Cumulative records of exercise responses from monkey 2N7. A typical baseline session as well as three drug sessions from experiment I (pyridostigmine,atropine, and 2-PAM) are shown; the 15-min adaptation period is not shown. Hash marks on the response lines denote food pellet delivery to the monkey.*

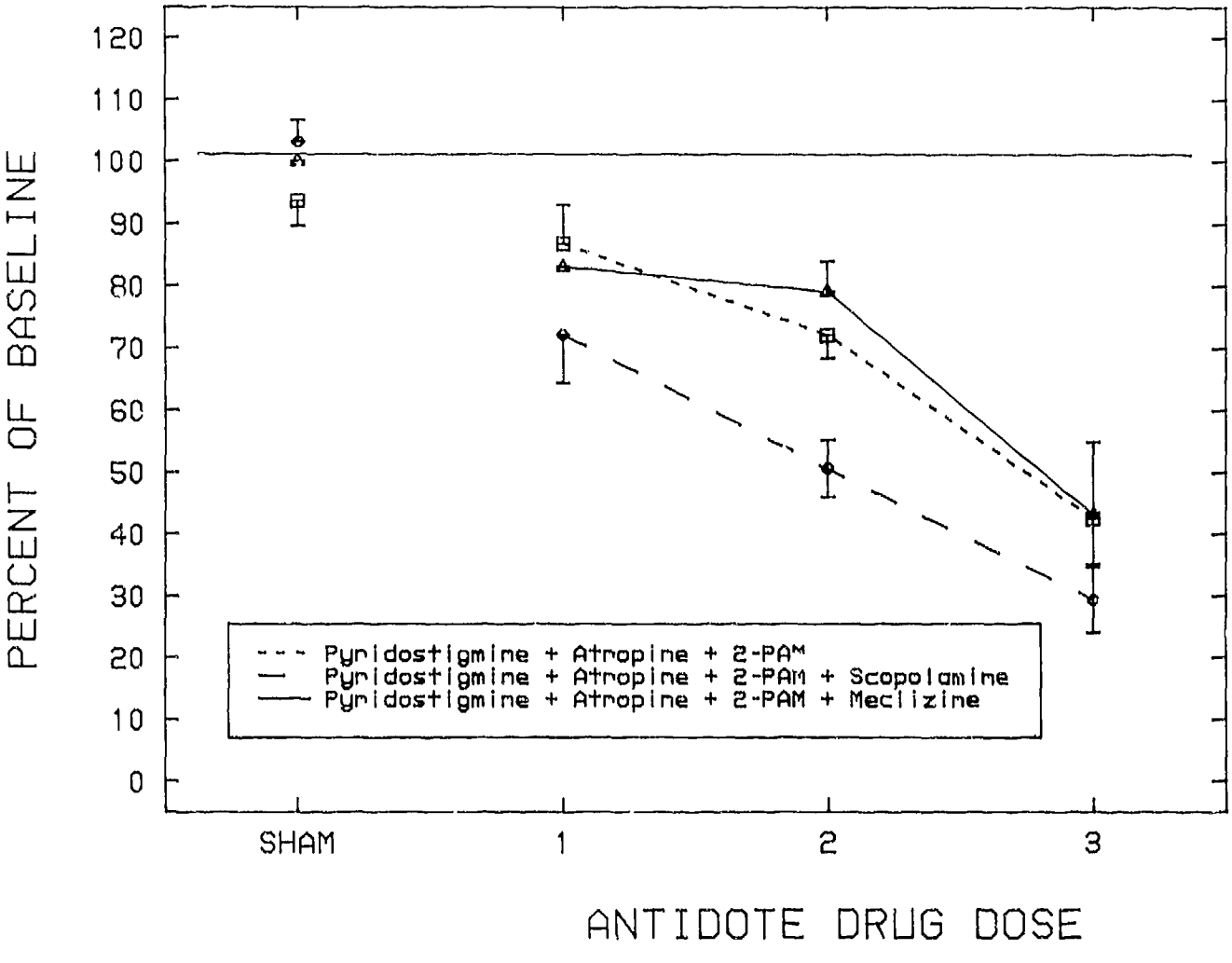


**Figure 4.** *Mean (± SEM) exercise responses during sham and concurrent drug for experiment I (n = 4). Atropine and 2-PAM were given in three different dosages.*

Mean postreinforcement pause times as a percentage of baseline times for the drug and sham sessions are shown in Fig. 5. The sham treatments did not significantly affect the pause times. The drug combinations again showed highly reliable effects for dosage, $F(3, 9) = 16.46, p < 0.001$, but drug combinations and interactions were not significant.

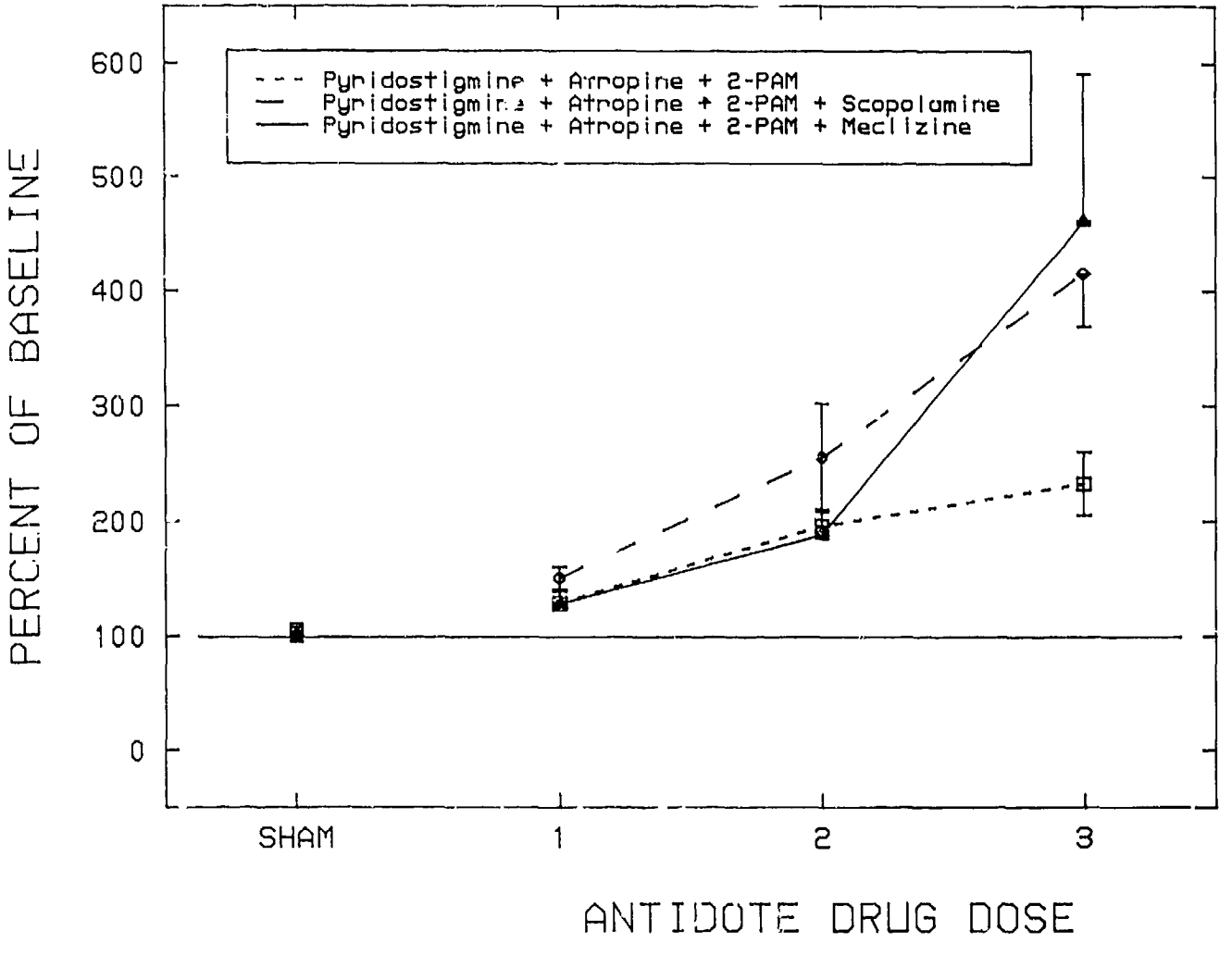


**Figure 5.** *Mean (± SEM) post reinforcement pause times during sham and concurrent drug exposure for experiment I (n = 4). Atropine and 2-PAM were given in three different dosages.*

Mean reaction times as a percentage of baseline reaction time for the drug and sham sessions are shown in Fig. 6. Neither the sham treatments nor the drug combinations produced significant differences in reaction time ($p > 0.05$).

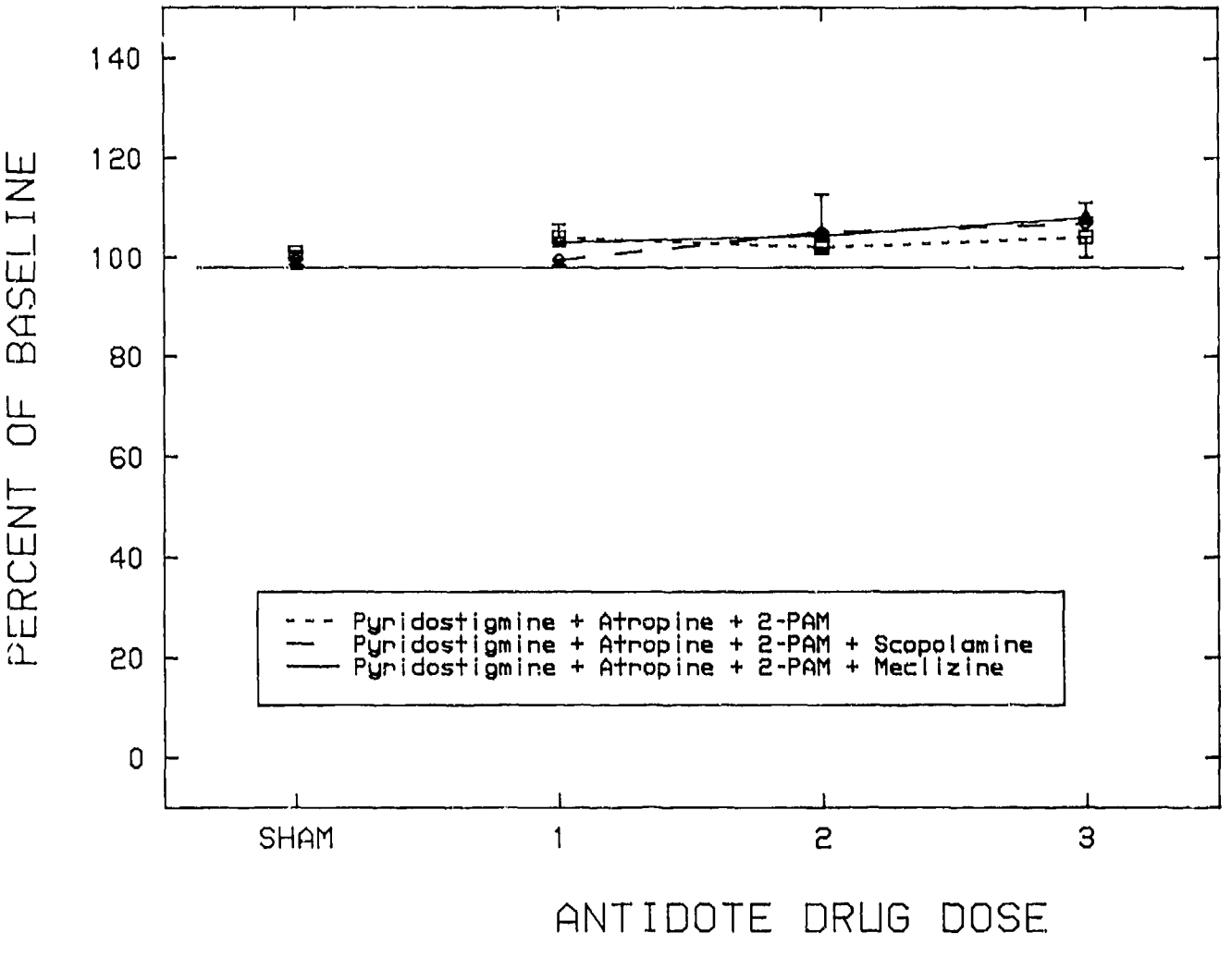


**Figure 6.** *Mean (± SEM) reaction times during sham and concurrent drug exposure for experiment I (n = 4). Atropine and 2-PAM were given in three different dosages.*

Experiment II. When the drugs were administered individually, only the anticholinergics atropine and scopolamine proved effective in disrupting monkey exercise responses. Mean exercise responses as a percentage of baseline illustrate this result in Fig. 7. The effects of sham treatments, the pretreatment drug pyridostigmine, and the therapeutic drugs scopolamine and meclizine are shown as the inset of Fig. 7. The sham treatments again did not significantly affect exercise rates. This experiment showed highly significant effects on exercise responses, $F(9, 27) = 9.80, p < 0.001$. Comparison of individual means showed that this effect was due to all three dosages of atropine and the single dosage of scopolamine, which differed significantly from the other drugs (meclizine, pyridostigmine, 2-PAM; $p < 0.05$).

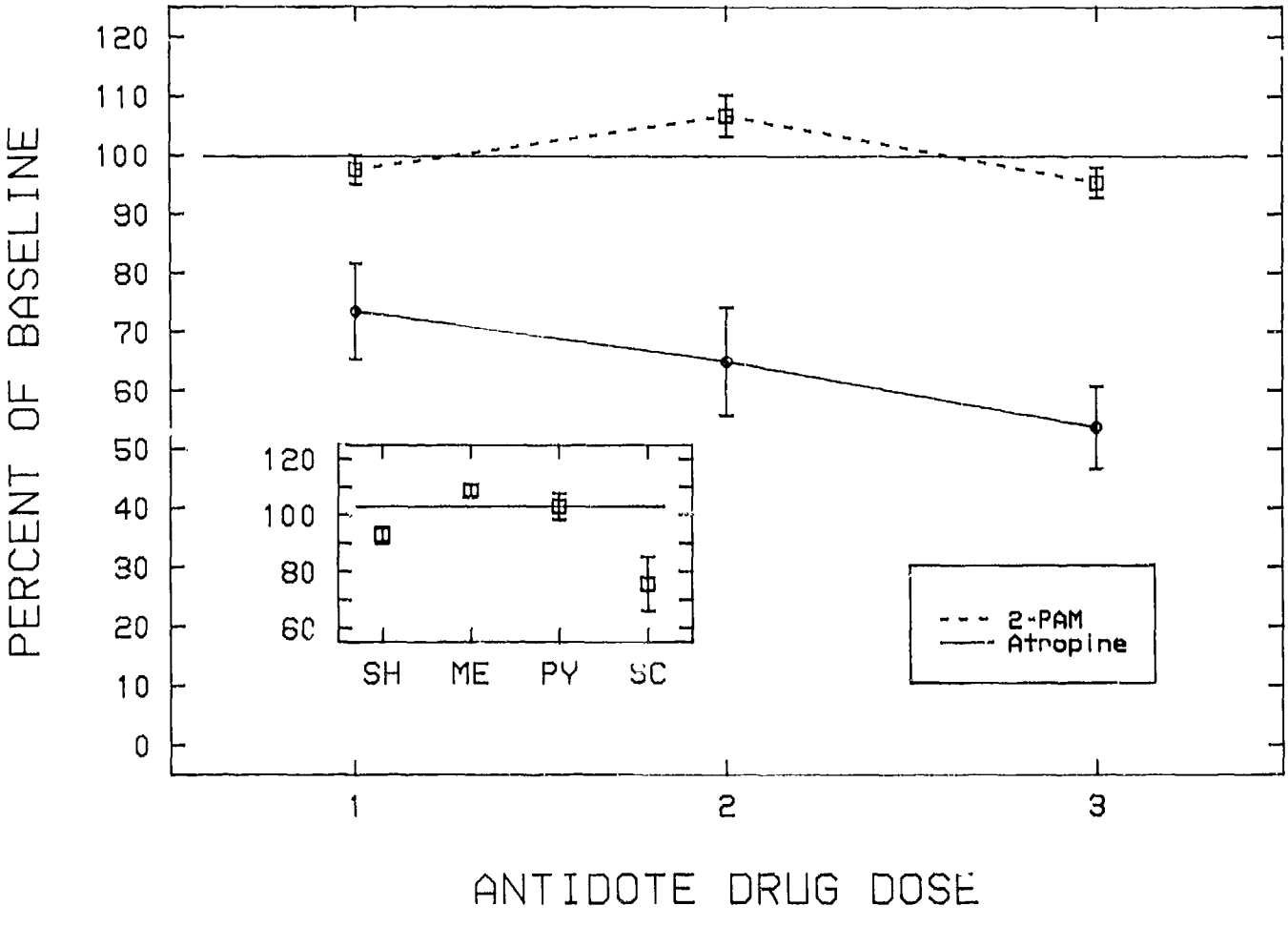


**Figure 7.** *Mean (± SEM) exercise responses during sham and individual drug exposure for experiment II (n = 4). The inset shows the effect of sham and the drugs meclizine, pyridostigmine, and scopolamine given individually.*

Mean postreinforcement pause times as a percentage of baseline times for the drug and sham sessions are shown in Fig. 8. The sham treatments did not significantly affect pause times. The single drug treatments again showed highly significant effects on postreinforcement pause times, $F(9, 27) = 12.28, p < 0.001$). Comparison of individual means showed that this effect was due to atropine.

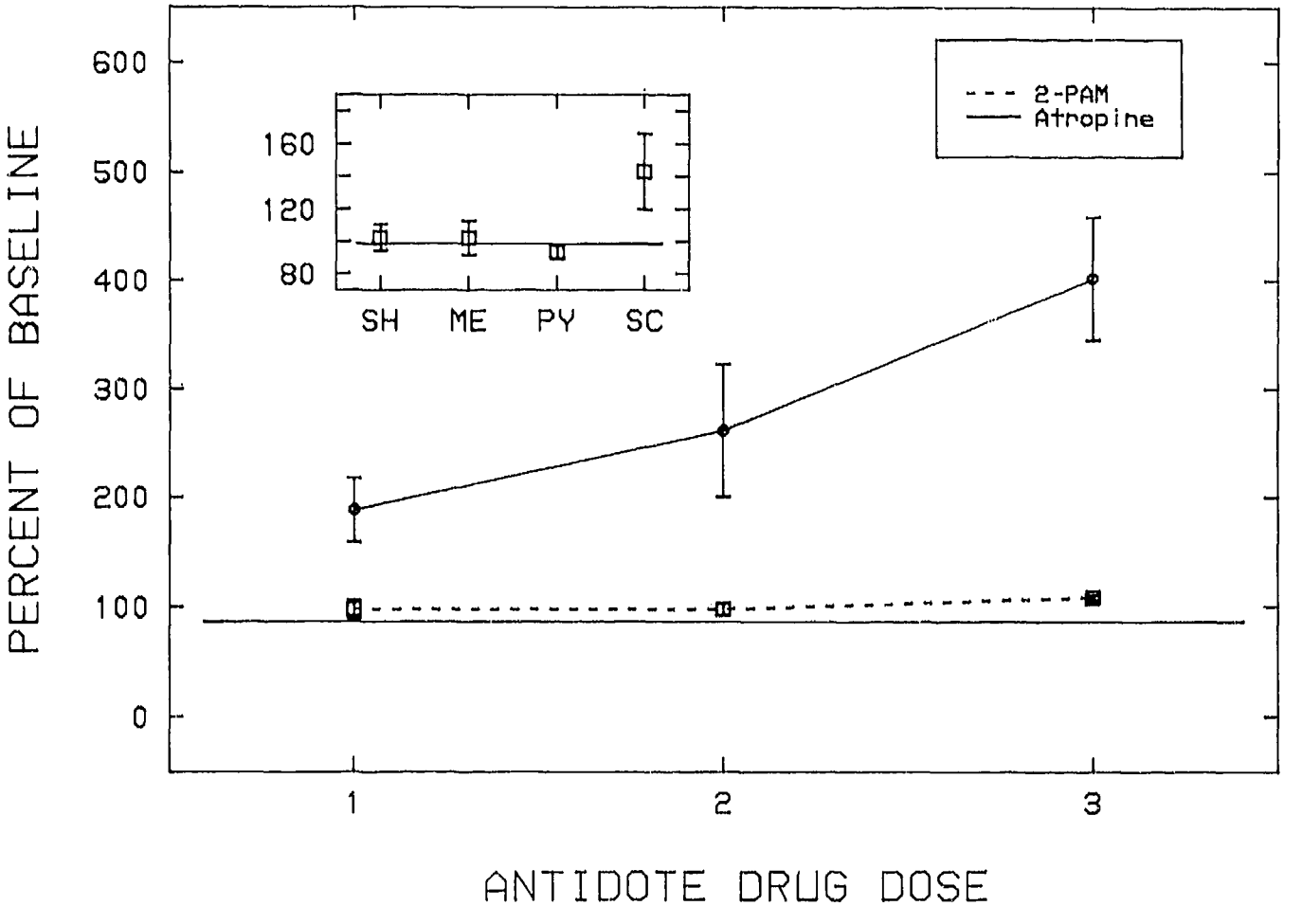


**Figure 8.** *Mean (± SEM) postreinforcement pause times during sham and individual drug exposure for experiment II (n = 4). The inset shows the effect of sham and the drugs meclizine, pyridostigmine, and scopolamine given individually.*

Mean reaction times as a percentage of baseline reaction time for the drug and sham sessions are shown in Fig. 9. The sham treatments and individual drugs again showed no significant effect on reaction time ($p > 0.05$).

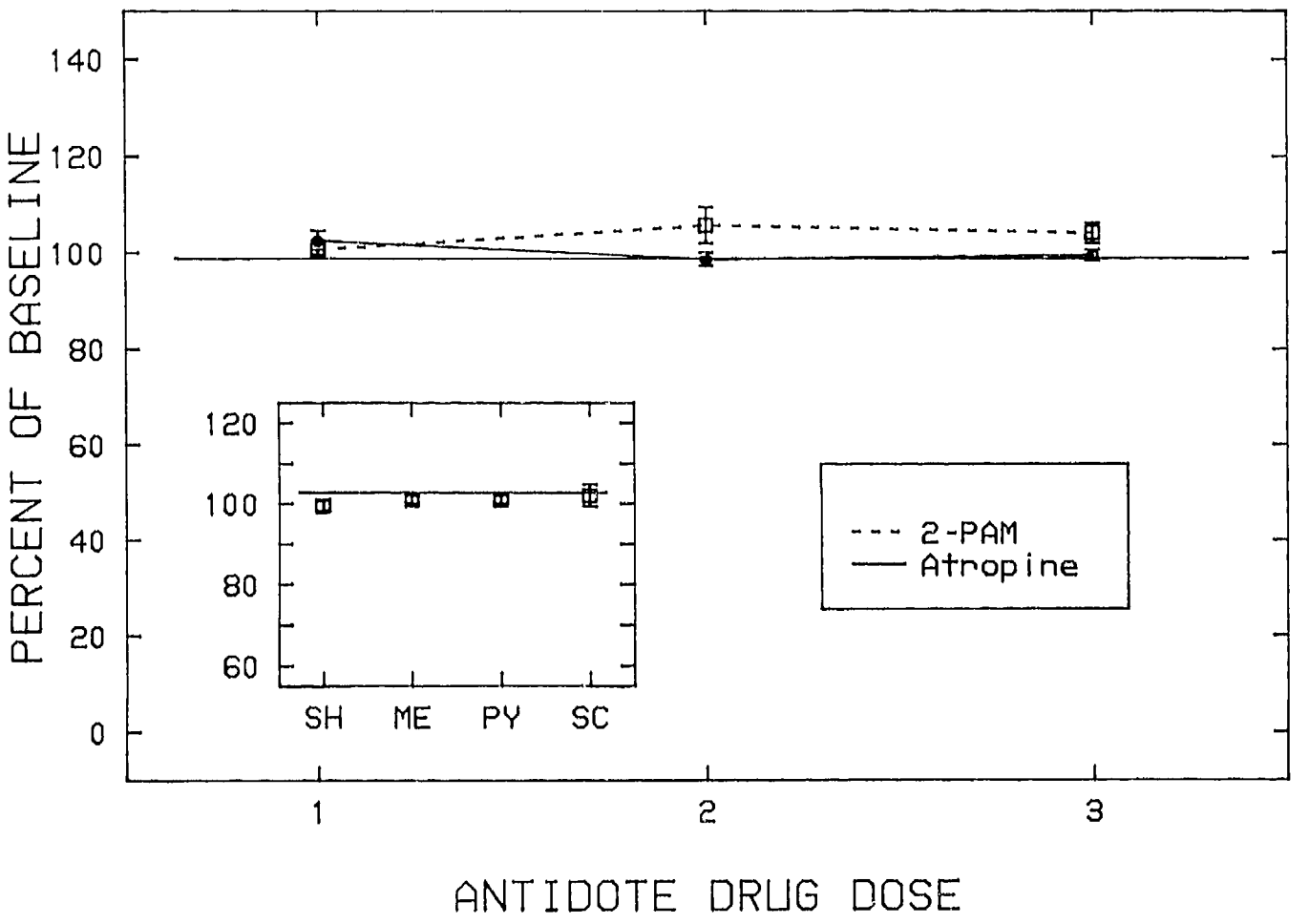


**Figure 9.** *Mean (± SEM) reaction times during sham and individual drug exposure for experiment II (n = 4). The inset shows the effect of sham and the drugs meclizine, pyridostigmine, and scopolamine given individually.*

Experiment III. During baseline sessions, each monkey typically consumed 350-500 ml of tap water. Compared to control sessions, water consumption did not increase significantly during drug sessions, $F(3, 9) = 1.37, p > 0.05$, and the effects of the drug combinations used in experiment I were not significantly altered. An example of this result is shown in Fig. 10, which compares mean exercise responses for this experiment (H2O-AVAILABLE) with mean exercise responses from experiment I (NO-H2O AVAILABLE group). Even with tap water available, the drug combinations still produced a significant decrement in exercise response, $F(3, 21) = 23.79, p < 0.001$, similar to that found in experiment I. Likewise, a significant alteration of postreinforcement pause times, $F(3, 21) = 5.50, p < 0.05$, occurred while reaction time remained unaltered, $F(3, 21) = 0.82, p > 0.05$.

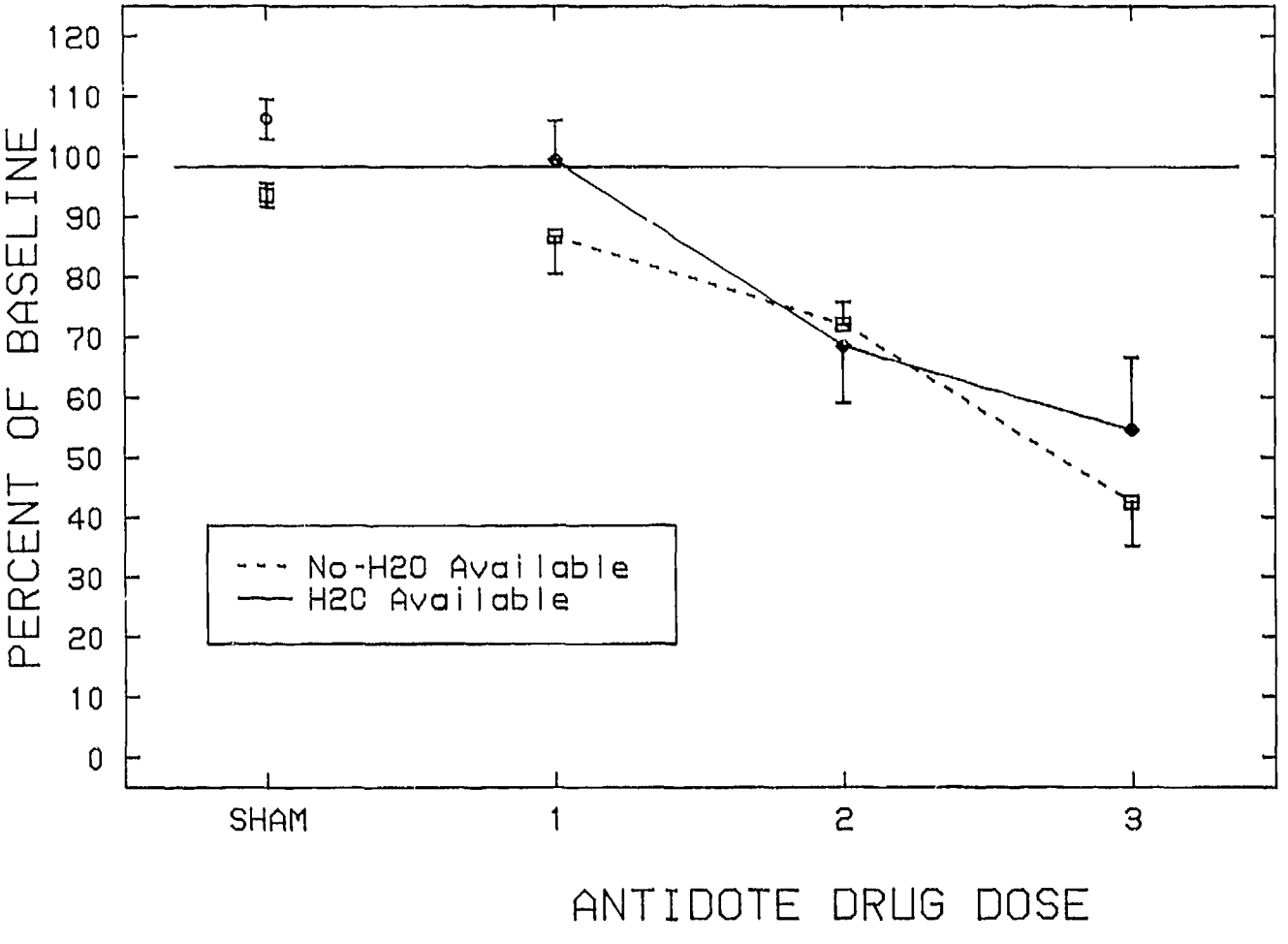


**Figure 10.** *Mean (± SEM) exercise responses during sham and concurrent drug exposure with water available to the monkeys (H2O AVAILABLE, n = 4) for experiment III. Also shown are the mean exercise responses from experiment I (NO-H2O AVAILABLE, n = 4).*

## Tail Temperature Effects

Experiment I. The mean ambient air temperature of the sound-attenuating chamber during drug sessions was 23.3 (± 0.17 *SEM*) °C at the start and 24.9 (± 0.15 *SEM*) °C at the end of the session. Tail temperature was sampled at the start of the session and at the start and end of each exercise component. At the start of control sessions, tail temperatures ranged from 22.9 to 30.5 ($M$ = 27.3 °C ± 0.41 *SEM*) and increased to a range of 30.5-34.6 ($M$ = 32.5 °C ± 0.18 *SEM*) by the end of the third exercise period. Tail temperatures, expressed as a percentage of baseline, are shown in Fig. 11. Sham drug exposures resulted in tail temperatures at or above baseline temperatures. In contrast, the tail temperatures for nearly all drug sessions were below baseline temperatures.

For the drug combination pyridostigmine, atropine, and 2-PAM (PR), the temperatures at the various drug doses were significantly different, $F(3, 9) = 6.27, p < 0.02$, while the interaction between sample time and drug dose was not ($p > 0.05$). Comparison of the means showed that dose 2 and dose 3 differed from sham at the end of exercise component 1 to the end of exercise component 3 ($p < 0.05$). The drug combination pyridostigmine, atropine, 2-PAM, and scopolamine, produced similar results: drug doses were significantly different, $F(3, 9) = 4.82, p < 0.01$, and the interaction between sample time and drug dose was not. Comparison of the means showed that temperatures at doses 2 and 3 dropped significantly during exercise component 1 and remained significantly below the sham group during exercise components 2 and 3 ($p < 0.05$). For the pyridostigmine, atropine, 2-PAM, and meclizine drug combination, significant differences were not observed. In general, when effects were observed, the largest drug dose produced the largest decrease in tail temperature as the session progressed.

Experiment II. The influence of atropine injections on tail temperatures was nearly the same as for the combined drug injections in which atropine was one of the drugs. Monkeys given single injections of atropine had tail temperatures significantly below baseline and sham values, depending on the drug dosage, although the two higher doses had about the same effect. This result is shown in the top panel of Fig. 12. The interaction of drug dose with sample time was significant, $F(15, 45) = 1.92, p < 0.05$. Comparison of the individual means showed that sham and dose 1 of atropine were significantly different from doses 2 and 3 at the end of the first exercise period through the end of the operant session. In contrast, tail temperature for the other drugs were not different from baseline performance or from the sham treatment although they were slightly elevated at the initial measurement in all conditions as is shown in the middle (2-PAM is PR) and bottom (pyridostigmine, scopolamine, and meclizine) panels of Fig. 12.

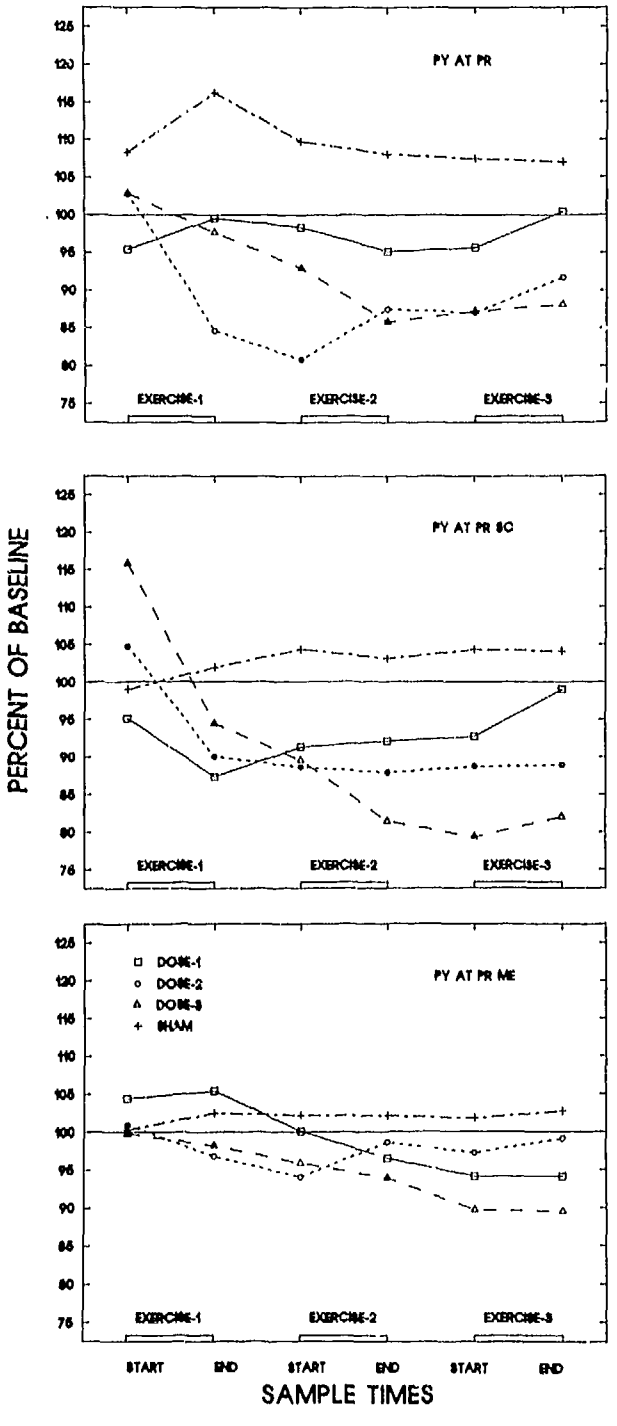


**Figure 11.** *Mean (± SEM) drug session tail temperatures as percent of baseline tail temperatures at the start and end of each exercise component of sham and concurrent drug sessions from experiment I (n = 4). Each panel shows the effect of a different drug combination at three dosages of atropine, 2-PAM (PR), and sham treatments.*

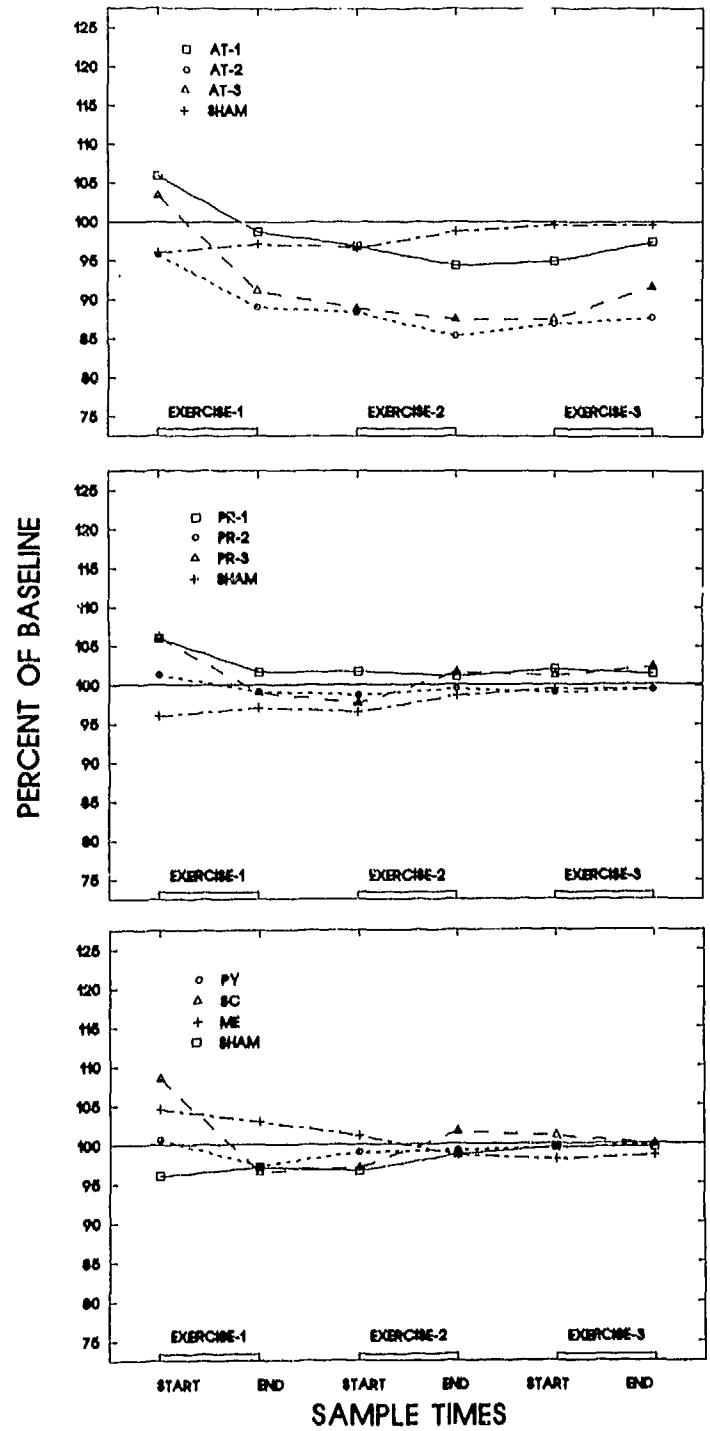


**Figure 12.** *Mean (± SEM) drug tail temperatures as percent of baseline tail temperatures at the start and end of each exercise component of sham and individual drug sessions from experiment II (n = 4). The top panel shows the effect of atropine at three dosages and sham treatments. The middle panel shows the effect of 2-PAM (PR) at three dosages and sham treatments. The bottom panel shows the effects of pyridostigmine, scopolamine, meclizine, and sham treatments.*

## DISCUSSION

The major findings of this study suggest that atropine at 0.03-0.09 mg/kg can significantly degrade physical exercise performance, but it has little effect on reaction time in a visually signaled task. In addition, exercise performance may be degraded further by scopolamine, but it is not influenced by 2-PAM, pyridostigmine, or meclizine. Tail temperatures were significantly reduced during atropine exposure, which suggests that the effects of atropine on exercise performance were not related to atropine impairment of thermoregulation (8,9).

The degrading effect of atropine on exercise performance was dose-dependent and replicable. The linear decrease of exercise responses from drug doses 1 through 3 was nearly the same in all three experiments. Except for scopolamine, the other drugs did not significantly affect exercise performance whether given with atropine or individually. The anticholinergics atropine and scopolamine were agonistic in their effect on exercise performance in both experiments I and II. The effect of atropine on postreinforcement pause time was also dose-dependent but differed in magnitude between experiments I and II. For example, when given in combination with pyridostigmine and 2-PAM, dose 3 of atropine in experiment I (see Fig. 5) doubled the postreinforcement pause times. In contrast, dose 3 of atropine given alone in experiment II (see Fig. 8) produced nearly a four-fold increase in postreinforcement pause time. One possiblity is that pyridostigmine or 2-PAM or both (experiment I) reduced the effect of atropine on postreinforcement pause time. Other factors such as age, endocrine status, or exercise fitness level could have modified the effects of atropine and produced the enhanced postreinforcement pause effect observed in experiment II. McMaster and Carney (10) have shown that chronic exercise can modify the response of rats to anticholinergic drugs. Our monkeys had completed experiment I and started experiment II within 10-15 sessions. They had already completed at least 150 exercise sessions before they started experiment II, so it seems unlikely that poor fitness level can account for this difference.

Sham drug exposures resulted in tail temperatures at or above baseline temperatures. In contrast, the tail temperatures for nearly all drug sessions that included atropine were below baseline temperatures. Because atropine significantly reduced exercise rates, core temperature, and tail temperature did not increase. In other words, exercise rate by the monkeys did not decrease due to an atropine-induced fever.

Previous animal studies have shown that anticholinergics disrupt schedule-controlled performance by producing dose-related decreases in response rates. For example, response rates and number of trials initiated decreased in rhesus monkeys given atropine on a differential reinforcement of low-rate (DRL) schedule (11) and delayed match-to-sample task (12). Atropine was given in much lower dosages in the present study. In addition, Penetar and McDonough (12) found disruption of short-term memory in monkeys given anticholinergic drugs. In rats, atropine-induced response rate decreases and alterations of temporal responding have been reported on DRL schedules at 6 and 12 mg/kg (13) and fixed-interval and fixed-ratio schedules at 2 and 4 mg/kg (14).

The mechanism of action by atropine to produce dose-related decrements in response rate is unknown. "Dry mouth," as a consequence of atropine-decreased salivary secretions, is one possible mechanism acting peripherally to produce the decrement in responding (14). Indeed, the large increases in postreinforcement pause times observed in this study seem to fit such a hypothesis, although, tap water consumption by the monkeys in experiment III of this study did not increase significantly. The exercise rate decrement

was the same as experiment I where tap water was not available. Furthermore, low doses of atropine actually decrease water intake in rats (15), a finding that is contrary to the "dry mouth" mechanism of behavioral action to explain the effects of atropine.

In conclusion, atropine (0.03-0.09 mg/kg) did not exert a global disruptive effect on behavioral performance. Exercise rates were decreased significantly by atropine, but atropine had little effect on the reaction time component of the operant schedule. More likely, atropine may exert a central effect on behavior, and this effect is selective for certain behaviors. Further research is necessary to elucidate more exact mechanisms of action.

## RECOMMENDATIONS

Premature use of atropine sulfate as a nerve-agent antidote may prove detrimental to physical performance of naval personnel. Although this drug did not alter reaction times of monkeys to simple visual stimuli, its effects on overall cognitive capability warrant further study.

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